Remarks

Claim Objection

Applicant has amended claim 12 to correct a minor typographical error and now requests withdrawal of the objection to claim 12 based on an informality.

Rejections under 35 U.S.C. § 112

Examiner rejected claim 18 for indefiniteness under 35 U.S.C. § 112, second paragraph, for use of the term "particularly." Applicant has rewritten this claim to avoid this term. Applicants request withdrawal of the rejection.

The Examiner rejected claims 10, 12, and 14-19 based on failure to comply with the enablement requirement under 35 U.S.C. 112, first paragraph. Claim 10 is amended herein and currently is drawn to a method of reducing the invasivity of cancer cells that are susceptible to AXL suppression comprising inhibiting AXL gene expression, AXL protein activity, interaction between AXL protein and its ligand, or a combination thereof.

The Examiner argues that one skilled in the art would not be able to predictably

1) reduce the invasivity of malignant disorders because the disclosure lacks *in vivo* data demonstrating the claimed method will function as a therapeutic cancer drug (OA p. 4, 11-12),
2) reduce invasivity of malignant disorders with an antibody directed against the Axl protein *in vivo* because the *in vitro* cell culture data is unreliable due to its artificial nature (OA p. 5, 8), and

3) reduce invasivity of malignant disorders by inhibiting *protein* function because the disclosure only provides measurement of Axl *mRNA* levels to determine the expression of the Axl protein are not correlative of protein levels (OA p. 4, 10).

The Examiner concludes that the specification provides insufficient guidance to one skilled in the art and undue experimentation would be required to practice the claimed invention. (OA p. 12-13).

Applicant has amended claim 10 herein to recite cancer cells that are susceptible to AXL suppression and to improve the readability of the language.

Contrary to the Examiner's assertions, the specification provides *in vivo* and reliable *in vitro* data to support the pending claims. The specification provides *in vivo* data from tumor cells subcutaneously implanted into nude mice (a reliable model) with subsequent intravital microscopy and histomorphological analyses. See Figure 9 and p. 13, line 20- p.14, line 16; p. 33, line 15 – p. 34, line 25, p. 35, line 24 – p. 36, line 13; Figure 11 and p. 15, lines 9-16 of the present specification. The results here showed impaired tumorigenicity, reduced tumor growth, lack of tumor invasion, and increased sensitivity towards serum withdrawal (apoptosis) after implantation of cells with a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain. See p. 32, line 22- p. 33, line 5; p. 33, line 15- p. 34, line 13; p. 38, lines 27-32 of the present specification. The *in vivo* data provide support that the claimed method will function as a therapeutic cancer drug.

Moreover, *in vitro* tests were conducted on Matrigel™-matrix (3D outgrowth), as described in the references 10[1], 11[2], and 12[3] cited in the present application, in order to show morphologies and to assay invasion activity and migration ability. These tests are described at p. 20, line 23 – p. 22, line 3; p. 25, line 19- p. 26, line 5 of the present application. See also p. 9, line 1-15 and Figure 1; p. 11, line 25- p. 13, line 4 and Figures 5-7. Reference 10, in particular, describes the benefits and accuracy of using a Matrigel™ for measuring invasiveness of tumor cells, showing that this model predicts *in vivo* behavior. These *in vitro* tests on Matrigel™ showed that the dominant negative mutant of the AXL gene (dnAXL) strongly suppressed invasiveness, migration and survival of cells and that a polyclonal antibody directed against the extracellular portion of the AXL protein strongly inhibited migration and invasion of tumor cells. See p. 26, lines 14-31. Applicant submits that the above testing, both *in vivo* and in an *in vitro* assay known in the art to reliably predict *in vivo* activity, show that the skilled person would have been able to practice the invention as claimed.

The specification also discloses data showing that inhibited AXL protein function resulted in reduced invasivity. For example, western blot analysis demonstrated that an antibody directed against the human AXL protein inhibits AXL-mediated signaling (see p. 13, lines 6-18 and Figure 8; p. 28, line 18- p. 29, line 7; p. 32, line 21 – p. 33, line 13). In addition, a truncated, dominant-negative mutant form of human UFO/AXL lacking the

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[1] Albini A. et al. A rapid in vitro assay for quantitating the invasive potential of tumor cells. Cancer Res., 47: 3239-3245, 1987

[2] Thompson E. W. et al. Association of increased basement membrane invasiveness with absence of estrogen receptor and expression of vimentin in human breast cancer cell lines. J. Cell. Physiol., 150: 534-544, 1992

[3] Terranova V.P., Hujanen E.S. Martin, G.R. Basement membrane and the invasive activity of metastatic tumor cells. J. Natl. Cancer Inst., 77: 311-316, 1986

intracellular RTK-bearing domain abolished Gas6/UFO/AXL-mediated signaling. See p. 13, lines 6-18; p. 32, line 21 – p. 33, line 13.

Thus, the application provides sufficient disclosure of reliable date, including *in vivo* data, to enable the invention. Applicant submits that the disclosures fully comply with the enablement requirement under 35 U.S.C. 112, first paragraph.

In view of the above remarks, Applicant requests reconsideration of the instant application and allowance of the claims as amended.

Respectfully submitted,

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